(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 2003/087094 A3

(51) International Patent Classification[7]: C07D 409/14, 405/12, 207/12, 409/04, A61K 31/4025, 31/40, A61P 13/10, 11/00, 1/00, C07D 417/14

(21) International Application Number:
PCT/EP2003/003786

(22) International Filing Date: 11 April 2003 (11.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
200200889 16 April 2002 (16.04.2002) ES

(71) Applicant *(for all designated States except US)*: **ALMIRALL PRODESFARMA S.A.** [ES/ES]; Ronda del General Mitre, 151, E-08022 Barcelona (ES).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **PRAT QUINONES, Maria** [ES/ES]; Calle Andrea Doria, 2, 1° 1a, E-08003 Barcelona (ES). **FERNANDEZ FORNER, Maria, Dolors** [ES/ES]; Calle Roger de Flor 221, 5° 4a, E-08025 Barcelona (ES).

(74) Agent: **SRINIVASAN, Ravi, Chandran**; J.A. Kemp & CO, 14 South Square, Gray's Inn, London WC1R 5JJ (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

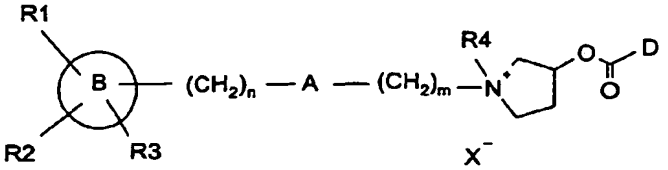
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
18 March 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRROLIDINIUM DERIVATIVES AS ANTAGONISTS OF M3 MUSCARINIC RECEPTORS



(I)

(57) Abstract: New pyrrolidinium derivatives having the chemical structure of general formula (I) are disclosed; as well as processes for their preparation, pharmaceutical compositions comprising them and their use in therapy as antagonists of M3 muscarinic receptors.

WO 2003/087094 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03786

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D409/14 C07D[redacted]12 C07D207/12 C07D409/04 [redacted]K31/4025
A61K31/40 A61P13/10 A61P11/00 A61P1/00 C07D417/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 956 062 A (LUNSFORD CARL D) 11 October 1960 (1960-10-11) cited in the application column 4, line 34; example 1 column 5, line 2; example 3 examples 19,24,31; table I column 8, line 7,8 column 2, line 5	1,20,21, 28
X	US 3 301 869 A (LUNSFORD CARL D) 31 January 1967 (1967-01-31) column 1, line 67 - line 72 example 14; table X	1,20,21, 28

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 January 2004	30. 01. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03786

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OGINO, YOSHIO ET AL: "Preparation of 2-aryl-2-hydroxyacetic acid ester derivatives as muscarinic M3 receptor antagonists" retrieved from STN Database accession no. 136:118468 XP002222161 CAS RN: 389888-86-2; 389890-38-4 abstract & WO 02 004402 A (BANYU PHARMACEUTICAL CO., LTD., JAPAN) 17 January 2002 (2002-01-17) -& EP 1 302 458 A (BANYU PHARMA CO LTD) 16 April 2003 (2003-04-16) claim 1	1,28
X	FR 2 155 927 A (SYNTHELABO) 25 May 1973 (1973-05-25) example 11 page 1, line 9,10 page 16, line 25 - line 31	1,21,28
Y	EP 0 863 141 A (BANYU PHARMA CO LTD) 9 September 1998 (1998-09-09) example 13 claims 1,5,6	1,28
Y	US 3 714 357 A (GUEREMY C ET AL) 30 January 1973 (1973-01-30) examples 1,11-18 column 15	1,28
Y	WO 01 04118 A (ALMIRALL PRODESFARMA SA ;BUIL ALBERO MARIA ANTONIA (ES); FERNANDEZ) 18 January 2001 (2001-01-18) claims 1,34,35	1,28
Y	FRANKO B V ET AL: "DERIVATIVES OF 3-PYRROLIDINOLS-III. THE CHEMISTRY, PHARMACOLOGY, AND TOXICOLOGY OF SOME N-SUBSTITUTED-3-PYRROLIDYL ALPHA-SUBSTITUTED PHENYLACETATES" JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 2, no. 5, 1960, pages 523-540, XP008021298 page 534 -page 539 examples 235,282,340,479,362,346,349,343	1,28

-/--

INTERNATIONAL SEARCH REPORT

	ional Application No
	rc1/EP 03/03786

C.(Continuation) DOCUMENTS CONSIDERED [redacted] BE RELEVANT

Category °	Citation of document, with indicati[redacted]ere appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 005, no. 148 (C-072), 18 September 1981 (1981-09-18) -& JP 56 079688 A (OTA SEIYAKU KK), 30 June 1981 (1981-06-30) abstract page 642	1,28
A	WO 98 21183 A (NOE CHRISTIAN R ;WAELBROECK MAGALI (BE); LAMBRECHT GUENTER (DE); C) 22 May 1998 (1998-05-22) claims 17,18; example 1	1,28

INTERNATIONAL SEARCH REPORT

International application No.
EP 03/03786

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 30 and 31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10,12-33 (all partially)

Compounds according to formula (I) of claim 1 in which B represents phenyl or biphenyl and D represents a group of formula i) as well as the process for their preparation according to claims 21, 22, and 25, their pharmaceutical use according to claims 26-33 and the intermediates 2-hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(2-phenoxyethyl)pyrrolidin-3-yl ester, 2-hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(3-phenoxypropyl)pyrrolidin-3-yl ester, 2-hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-phenethylpyrrolidin-3-yl ester of claim 23 and (3R)-1-(3-phenoxypropyl)pyrrolidin-3-ol of claim 24.

2. Claims: 1-9,11-14,17-22,25-33 (all partially)

Compounds according to formula (I) of claim 1 in which B represents phenyl or biphenyl and D represents a group of formula ii) as well as the process for their preparation according to claims 21, 22, and 25, and their pharmaceutical use according to claims 26-33.

3. Claims: 1,2,4-7,10,12-18,21,22,25-33 (all partially)

Compounds according to formula (I) of claim 1 in which B represents naphthalenyl or 5,6,7,8-tetrahydronaphthalenyl and D represents a group of formula i) as well as the process for their preparation according to claims 21, 22, and 25, and their pharmaceutical use according to claims 26-33.

4. Claims: 1,2,4-7,11-14,17,21,22,25-33 (all partially)

Compounds according to formula (I) of claim 1 in which B represents naphthalenyl or 5,6,7,8-tetrahydronaphthalenyl and D represents a group of formula ii) as well as the process for their preparation according to claims 21, 22, and 25, and their pharmaceutical use according to claims 26-33.

5. Claims: 1-10,12-33(all partially)

Compounds according to formula (I) of claim 1 in which B represents benzo[1,3]dioxolyl or a heteroaromatic group and D represents a group of formula i) as well as the process for their preparation according to claims 21, 22, and 25, their pharmaceutical use according to claims 26-33 and the

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

intermediates 2-hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-yl ester of claim 23 and (3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-ol of claim 24

6. Claims: 1-9,11-14,17,18,21,22,25-33 (all partially)

Compounds according to formula (I) of claim 1 in which B represents benzo'1,3!dioxolyl or a heteroaromatic group and D represents a group of formula ii) as well as the process for their preparation according to claims 21, 22, and 25, and their pharmaceutical use according to claims 26-33.

INTERNATIONAL SEARCH REPORT

Int[illegible]al Application No
PCT/EP 03/03786

Patent document cited in search report		[illegible]lication date	Patent family member(s)		Publication date
US 2956062	A	11-10-1960	NONE		
US 3301869	A	31-01-1967	NONE		
WO 02004402	A	17-01-2002	AU	7102701 A	21-01-2002
			CA	2415468 A1	10-01-2003
			EP	1302458 A1	16-04-2003
			WO	0204402 A1	17-01-2002
FR 2155927	A	25-05-1973	FR	2155927 A1	25-05-1973
EP 0863141	A	09-09-1998	AT	205490 T	15-09-2001
			AU	7145996 A	30-04-1997
			DE	69615214 D1	18-10-2001
			DE	69615214 T2	27-06-2002
			EP	0863141 A1	09-09-1998
			US	6130232 A	10-10-2000
			CA	2234619 A1	17-04-1997
			WO	9713766 A1	17-04-1997
US 3714357	A	30-01-1973	AT	291272 B	12-07-1971
			BE	735031 A	01-12-1969
			CH	513174 A	30-09-1971
			DE	1935751 A1	26-02-1970
			FR	2012964 A5	27-03-1970
			GB	1219606 A	20-01-1971
			NL	6910859 A ,B	19-01-1970
			SE	361314 B	29-10-1973
WO 0104118	A	18-01-2001	ES	2165768 A1	16-03-2002
			AT	235492 T	15-04-2003
			AU	6433000 A	30-01-2001
			BG	106301 A	30-08-2002
			BR	0012434 A	02-04-2002
			CA	2381165 A1	18-01-2001
			CN	1373760 T	09-10-2002
			CZ	20020121 A3	13-11-2002
			DE	60001840 D1	30-04-2003
			DE	60001840 T2	11-12-2003
			DK	1200431 T3	21-07-2003
			EE	200200017 A	15-04-2003
			WO	0104118 A2	18-01-2001
			EP	1200431 A2	02-05-2002
			ES	2193098 T3	01-11-2003
			HK	1042487 A1	18-07-2003
			HU	0202100 A2	28-10-2002
			JP	2003504368 T	04-02-2003
			NO	20020180 A	13-03-2002
			PT	1200431 T	31-07-2003
			SI	1200431 T1	31-10-2003
			SK	432002 A3	01-04-2003
			TR	200200768 T2	22-07-2002
			US	2003055080 A1	20-03-2003
			ZA	200200232 A	10-04-2003
JP 56079688	A	30-06-1981	NONE		
WO 9821183	A	22-05-1998	WO	9821183 A1	22-05-1998

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 03/03786

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9821183 A		AT	238280 T	15-05-2003
		AU	745331 B2	21-03-2002
		AU	4856097 A	03-06-1998
		CA	2271276 A1	22-05-1998
		CN	1237159 A	01-12-1999
		DE	59709927 D1	28-05-2003
		DK	937041 T3	11-08-2003
		EP	1371645 A1	17-12-2003
		EP	1369414 A1	10-12-2003
		EP	0937041 A1	25-08-1999
		ES	2195121 T3	01-12-2003
		HU	9903791 A2	28-03-2000
		JP	2001504459 T	03-04-2001
		NO	991056 A	11-05-1999
		NZ	336202 A	27-10-2000
		PL	332595 A1	27-09-1999
		PT	937041 T	30-09-2003
		SI	937041 T1	31-10-2003
		US	6307060 B1	23-10-2001
		US	2003220400 A1	27-11-2003
		US	2002173536 A1	21-11-2002